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Management of Pituitary Adenomas

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Summary: We present an overview of the management of pituitary adenomas, with discussions of microanatomy, of diagnostic studies of general neuroendocrine function, and of radiologic evaluation. We discuss the diagnosis of pituitary adenoma and its treatment with sections on null cell, prolactin (PRL)-secreting, growth hormone (GH)-secreting, and corticotropin-secreting adenomas and on other secreting tumors. For surgical management, we present an historical background and then focus on the transsphenoidal and transcranial approaches. The use of primary and postoperative radiotherapy (RT) is examined. **Key Words:** Pituitary adenoma—Prolactin—Growth hormone—Corticotropin—Transsphenoidal surgery—Transcranial surgery.

Pituitary adenomas are benign tumors that may originate from any of the native pituitary cell types. Pituitary adenoma is a common incidental sellar abnormality; autopsy and radiographic studies suggest that incidental microadenomas (lesions <10 mm in diameter) may be present in 10 to 20% of the population, but that macroadenomas (>10 mm) are rare. Contemporary imaging modalities, combined with the advent of the radioimmunoassay, have ushered in a new era in the diagnosis and management of pituitary adenomas. Such contemporary diagnostic studies have rendered original morphometric histological classifications of pituitary tumors clinically obsolete.

MICROSCOPIC ANATOMY

Normal Anatomy and Physiology of the Adenohypophysis

The anterior pituitary contains connective tissue, fenestrated capillaries, and epithelial cells organized in a glandular pattern (1–3). A description of the way distinct epithelial cell types may be characterized by their secretory protein hormones follows.

Growth Hormone Producing Cells

Somatotrophs, growth hormone (GH)-producing cells of the pituitary gland, comprise ~50% of the normal adenohypophyseal cell population and are located in the lateral wings of the anterior lobe (3–4). GH is a 191 amino acid polypeptide hormone that opposes the effect of insulin, stimulates the uptake of amino acids, and causes a release of free fatty acids from tissue storage sites (5). In the liver and other tissues, GH also mediates the synthesis of insulin-like growth factors (IGFs), previously called somatomedins, that induce protein synthesis in the skeleton and muscle and glucose oxidation in adipose tissue. IGFs also stimulate cell replication at these sites. The secretion of GH is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin. GH and insulin-like growth factor-1 (IGF-1) (also called somatomedin-C) stimulate the release of somatostatin, thereby down-regulating the secretion of GH. GH is se-

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creted in episodic surges occurring every 3 to 4 h; in young individuals, the greatest peaks occur after the onset of deep sleep. Stimuli of GH secretion include insulin-induced hypoglycemia, arginine, exercise, L-dopa, clonidine, propanolol, and GHRH.

Prolactin-Producing Cells

The mammotropes, also called lactotropes, represent 15 to 25% of the anterior pituitary cells and populate the lateral gland (6,7). These cells increase during pregnancy and lactation and following estrogen therapy. Prolactin (PRL) is a 198 amino acid polypeptide known to facilitate the development of breast tissue to ensure the production of milk. PRL secretion is stimulated by thyrotropin-releasing hormone (TRH), estrogens, stress, and exercise. Dopamine is acknowledged to be the principal prolactin inhibitory factor.

Adrenocorticotropin-Producing Cells

Corticotrophs constitute ~20% of the adenohypophyseal cells. They lie within the mediolateral aspects of the pars distalis (3,8). Adrenocorticotropin (ACTH) is a 39 amino acid peptide that promotes growth of the adrenal cortex and the synthesis of hormones produced by this gland. ACTH also has melanotropic effects and is responsible for the pigmentation commonly seen in Nelson's syndrome and Addison's disease. ACTH is a fragment of proopiocortin. Both the corticotropic and the melanotropic cells cleave the pro-hormone into a common precursor containing 130 amino acids. Within the corticotroph there is further cleavage to form ACTH (1–39 amino acids) and β-lipotropin (β-LPH) (1–91 amino acids). Within the melanotroph, ACTH is cleaved into alpha-melanostimulating hormone (α-MSH) (1–13 amino acids) and corticotropin-like intermediate peptide; β-LPH is cleaved further to form gamma-LPH (1-58 amino acids) and β-endorphin (61–91 amino acids). In the human, the physiological roles of the lipotropins, α-MSH, and β-endorphin, are unclear. The synthesis and secretion of ACTH is stimulated by corticotropin-releasing hormone (CRH). Vasopressin, though a weak ACTH stimulant, directly potentiates the effect of CRH. The inhibition of ACTH release is regulated by the negative feedback effect of cortisol on the corticotroph directly and on the release of CRH at the hypothalamus. ACTH also regulates the release of CRH through a short loop negative feedback effect. The secretion of ACTH follows a circadian rhythm and occurs in brief episodes during the late sleep period and just before awakening. Rapid release of ACTH also occurs under the stimulation of stress such as pain, fear, noise, extreme cold, fever, hypoglycemia, and hemorrhage.

Thyroxin-Stimulating Hormone-Producing Cells

Thyrotrophs constitute ~5% of the adenohypophysis and are located in the anteromedial region (3,9). TSH is a glycoprotein composed of two noncovalently linked moieties, the alpha and the beta subunits. The beta subunit confers biological activity on the hormone. Thyrotrophs secrete not only TSH but also the separate subunits. TSH regulates the synthesis of thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), by the thyroid gland. A euthyroid state is maintained through a balance between the stimulatory effect of thyrotropin-releasing hormone (TRH) produced by the hypothalamus and the negative feedback inhibition of the thyroid hormones on the thyrotroph cells and on hypothalmic TRH-producing cells.

Gonadotropic Hormone-Producing Cells

Gonadotrophs secrete both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and occupy ~10% of the anterior gland within its medial region (3,8). FSH and LH are glycoproteins formed by two noncovalently linked subunits, the previously mentioned common α-subunit and the specific β-subunit, which confers the biological activity on the hormones. Gonadotropin levels are elevated during the first 1 to 2 years of life and rise again with the onset of puberty. FSH stimulates ovarian follicular growth in the female and testicular growth and spermatogenesis in the male. In the female, LH promotes ovulation and luteinization of the ovarian follicle and enhances estrogen and progesterone production by the ovary. In the male, LH supports interstitial (Leydig) cell function and hence the production of testosterone by the testicle. Gonadotropin secretion in the ovulating female is stimulated by gonadotropin-releasing hormone (GnRH) and both positively and negatively regulated by the gonadal steroids. Short-term effects of estrogens are suppressive on basal LH release. With longer duration of exposure to estrogens, particularly at low doses, gonadotropin secretion is enhanced. In males, testosterone has a negative feedback effect

on hypothalamic GnRH and on the pituitary gonadotroph cells.

Normal Anatomy of the Neurohypophysis

The posterior pituitary lacks a blood-brain barrier and consists of hypothalamic-originating neuronal axons and terminals, specialized glial cells, and blood vessels. It is subdivided into three anatomical regions: the median eminence, the infundibular stem, and the neural lobe (10,11).

DIAGNOSTIC STUDIES

The evaluation of the anterior pituitary is indicated in patients who present signs or symptoms compatible with isolated or multiple hormonal deficits, hyperprolactinemia, GH excess, hypercortisolism, hyperthyroidism, diabetes insipidus (DI), a hypothalamic disorder, or with symptoms of any sellar or suprasellar mass. Complete examination of sellar and parasellar regions encompasses both neuroendocrine and anatomical (radiographic) evaluations.

General Neuroendocrine Evaluation

Anterior Pituitary

As mentioned previously, the advent of radioimmunoassay and other immunohistochemical methods have greatly enhanced our understanding of the function of the pituitary gland in normal and pathological states (12–16). The diagnostic tests most commonly used to evaluate hypothalamic-pituitary function are listed in Table 1. In addition to recognizing any hypersecretory syndromes associated with a pituitary adenoma, recognition of hypopituitarism before any surgical endeavor is imperative; this may prevent complications in the perioperative period (see details herein). A screening neuroendocrine evaluation should include measurement of thyroid, corticosteroid, PRL, gonadotropic, and somatotropic hormone function.

TSH deficiency can be diagnosed by simultaneously measuring basal serum TSH and thyroid hormone levels. A low serum T_4 in the presence of an inappropriately low TSH level suggests a central cause of hypothyroidism. To distinguish a hypothalamic from a pituitary defect, the TSH reserve within the thyrotrophs may be assessed by performing a TRH test. In the intact pituitary, TSH and PRL rise in response to TRH stimulation, and GH falls. TSH oversecretion, as in the context of a rare functional tumor, results in high circulating levels of both TSH and T_4.

TABLE 1. *Diagnostic tests to evaluate hypothalamic-pituitary hypofunction*

Thyroid
Serum TSH, T_4, T_3RU
TRH stimulation test (measure serum TSH, prolactin, GH)
Adrenal
Serum cortisol (8 a.m.)
Plasma ACTH (if serum cortisol low)
CRH stimulation test (measure serum ACTH)
Sex hormones
Serum testosterone (men), estradiol (amenorrheic premenopausal women)
Serum LH, FSH
GnRH stimulation test (measure serum LH and FSH)
Serum prolactin
Growth hormone
Serum IGF-1 and growth curve (children and adolescents)
GH stimulation tests (GHRH, arginine, clonidine, propranolol, L-dopa, insulin-hypoglycemia, exercise)

TSH, thyrotropin; T_4, thyroxine; T_3RU, triiodothyronine resin uptake; TRH, thyrotropin-releasing hormone; GH, growth hormone; ACTH, corticotropine; CRH, corticotropine releasing hormone; LH, luteinzing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor-1; GHRH, growth hormone-releasing hormone.

Dynamic tests are required to diagnose a state of ACTH deficiency because the morning cortisol is persistently low only when the ACTH deficiency is very severe. The CRH test distinguishes a hypothalamic CRH deficiency from a pituitary ACTH deficiency. The absence of ACTH responsiveness to CRH is diagnostic of a pituitary corticotroph deficiency. The insulin-induced hypoglycemia and the glucagon test stimulate the entire hypothalamic–hypophyseal adrenal axis. The ACTH stimulation test evaluates the capacity of the adrenals to secrete cortisol.

Gonadotropin deficiency can be diagnosed by simultaneously measuring basal serum FSH and LH levels and gonadal steroids, estradiol in the premenopausal female, and testosterone in the male. In the event of primary gonadal failure, the lack of negative feedback by the gonadal steroids on the hypothalamic GnRH and pituitary LH- and FSH-secreting cells leads to an elevation of LH and FSH. Low circulating gonadal steroids associated with inappropriately low gonadotropin levels suggest a hypothalamic or pituitary disturbance. The GnRH stimulation test evaluates pituitary gonadotroph function. Lack of response of LH and FSH to GnRH indicates a lesion at the pituitary rather than

the hypothalamic level. However, when the pituitary gonadotroph cells has not been stimulated by hypothalamic GnRH for a prolonged period of time, repetitive GnRH stimulation may be necessary to elicit a secretory response.

GH levels in the basal state are often low in normal individuals. The measurement of the plasma IGF-1 level permits a more accurate diagnosis of a GH deficient state as it reflects the 24-h secretion of GH. Stimulatory tests to assess the somatotroph function include sleep and exercise studies; insulin-induced hypoglycemia; and administration of arginine, L-dopa, clonidine, propranolol, or GHRH. GH hypersecretion can be assessed by measuring the IGF-1 level (best screening test) and by performing a glucose suppression test, in which event the plasma glucose does not suppress below 2 μg/L (see herein).

Posterior Pituitary

Central DI refers to a state of relative or absolute insufficient secretion of vasopressin from the posterior pituitary gland (17–20). This must be differentiated from renal DI in which the kidney fails to respond to an appropriate elevation in serum vasopressin. The diagnosis of central DI may be established by the water deprivation test. This study assesses the patient's ability to concentrate the urine in response to an increase in plasma osmolality. Both hypothyroidism and hypocortisolism may cause a decrease in the glomerular filtration rate and thus mask a state of DI. Therefore, prior to the test, the patient should be in a euthyroid state, and adrenal insufficiency, if present, should be corrected. During the test, the diagnosis of DI is based on the development of abnormally concentrated plasma (osmolality > 300 mOsmol/kg) and urine that remains dilute (osmolality <270 mOsmol/kg). Also, the urine volume is not reduced to the expected degree. At the end of the water deprivation period (when two serial urine osmolalities vary by <30 mmol/kg or when 3 to 5% of the body weight has been lost), the administration of exogenous vasopressin will correct these abnormalities (in contrast to renal DI, in which there is resistance to exogenous vasopressin).

Radiographic Evaluation

Radiographic examination of the pituitary should provide information about the bony anatomy of the sella and its surroundings in addition to intrasellar contents.

For the diagnosis and management of pituitary tumors, magnetic resonance imaging (MRI) has had a revolutionary impact. MRI is superior to computed tomography (CT) because of its inherently greater soft tissue contrast, which allows clear visualization of the optic chiasm, optic nerves, cavernous sinuses, and carotid arteries (21–28). High field thin section MRI appears to be the most sensitive imaging method for preoperative localization of pituitary adenomas. On unenhanced images, focal glandular hypointensity identified on coronal images is the most sensitive predictor of adenoma location. Radiographic evaluation should consist of coronal, sagittal, and axial MRI, with large tumors usually having similar signal intensity to brain on T1-weighted images. The normal pituitary gland, infundibulum, and cavernous sinuses enhance immediately after administration of gadolinium-DTPA, allowing contrast between the enhancing normal glandular tissue and the low-intensity adenomas. Currently, a T1-weighted image following the infusion of gadolinium-diethylenetriaminepentoacetic acid (DTPA) is the method of choice for the delineation of intrasellar pathology. Shortly after administration, the normal vascular pituitary increases in signal intensity (25), and a pituitary tumor contrasts by remaining less intense, being slower to perfuse with the contrast agent (Fig. 2). However, after sufficient time for dye uptake into the tumor, the tumor increases in signal intensity accordingly. Following this, the normal surrounding pituitary "washes out" the contrast before the tumor. Thus, the reverse situation prevails, and the tumor remains higher intensity than the surrounding gland for a period of time. The optimal and most consistent time for visualization is therefore in the early postinfusion period because the kinetics of dye perfusion and clearance may be variable among patients. MRI also offers visualization of the major vessels, specifically the intracavernous carotids, indicating the proximity of these structures to the tumor. Such visualization is especially important in the rare case of the presence of severely ectatic carotid arteries that might preclude a transnasal surgical approach for risk of vascular injury.

If MRI is not available, CT may be done, performing direct coronal cuts, or with coronal and sagittal reconstruction of axial sections through the sellar region. On unenhanced CT, a pituitary tumor usually has density slightly less than surrounding

pituitary or cavernous sinuses. Adenomas may be homogeneous, contain low-density regions of necrosis or cyst formation, or demonstrate intratumoral hemorrhage or calcification. Such a study may also offer relevant information regarding the bony landmarks by varying the window widths and may reveal sellar enlargement, or sloping, thinning, or erosion of the sellar floor, all indicative of an intrasellar expansile process. In addition, the presence of calcium in some sellar or parasellar lesions (e.g., craniopharyngioma, meningioma) may be better visualized on CT images, therefore providing information supplemental to that obtained by MRI (28–30).

DIAGNOSIS OF PITUITARY TUMORS AND THEIR TREATMENT

Currently, these tumors are classified according to their hormone production (if any) (31) (Table 2). Hormone production and secretion by an adenoma may be asymptomatic, but this information is nonetheless helpful in the characterization of an incidental mass on MRI. Moreover, it has recently been appreciated that multiple hormones may be secreted by some tumors (plurihormonal lesions), which may complicate this classification (32). A further complicating factor lies in the definition of the term "hormone production." Classically, as cell biologists and pathologists define production as hormone *synthesis* not necessarily associated with (or followed by) hormone *release*, the histology of the particular tumor may not correlate with the clinical endocrinological status of the patient. From a clinical perspective, the true secretion of the hormone is important; it determines any hypersecretory endocrinopathy, and thus provides a serum parameter for clinical diagnosis and response to treatment.

TABLE 2. *Pituitary adenoma types and their incidence*

Type	Incidence (%)	
GH-cell adenoma	15.1	
Densely granulated		7.1
Sparsely granulated		8.0
PRL-cell adenoma	28.0	
Densely granulated		0.5
Sparsely granulated		27.5
ACTH-cell adenoma	13.8	
Endocrinologically active		8.1
Silent		5.7
TSH-adenoma	0.6	
FSH/LH adenoma	4.4	
Null cell adenoma	24.7	
Nononcocytotic		17.4
Oncocytotic		7.3
Plurihormonal adenoma	13.4	
GH-cell PRL-cell adenoma		5.2
Acidophil stem cell adenoma		2.5
Mammosomatotroph cell adenoma		1.4
Other		4.3
Total	100.0	

GH, growth homrone; PRL, prolactin; ACTH, corticotropin; TSH, thyrotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

From Kovacs K, Horvath E. Pathology of pituitary adenomas. In: Collu R, Brown GM, Van Loon GR, eds. Clinical neuroendocrinology. Boston: Blackwell Scientific Publications, 1988, with permission.

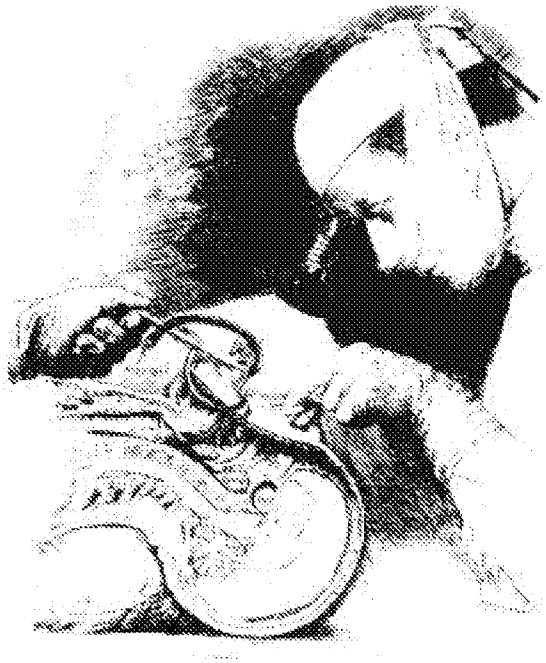

FIG. 1. Cushing's adaptation of the transphenoidal technique. This 1912 drawing by the renowned medical illustrator Max Brödel shows the technique of transsphenoidal approach to the hypophysis. Note the sublabial incision adopted by Cushing at the time. (From Cushing H. The Weir Mitchell Lecture. Surgical experiences with pituitary disorders. *JAMA* 1914;63:1515–25).

Null Cell Adenomas

Clinical Manifestations and Diagnosis

Although tumors that secrete any of the anterior pituitary hormones may grow to sufficient size to become macroadenomas, nonfunctioning adenomas more frequently present with symptoms of larger lesions, such as visual failure or hypopituitarism. Statistically, null cell tumors are among the most common kind of adenoma found in the pituitary and

present more frequently later in life than secreting tumors. The classic visual triad produced by larger tumors is characterized by optic disc pallor, loss of central visual acuity, and visual field defects (bitemporal hemianopsia) (33).

In the endocrinological evaluation of the patient suspected of harboring a nonfunctioning pituitary tumor, an important diagnostic pitfall to be avoided is the misdiagnosis of a PRL-secreting tumor. Larger adenomas comprised of cells other than lactotrophs may produce a mild to moderate hyperprolactinemia from the so-called "stalk-section effect" [disconnection hyperprolactinemia-stalk compression causing loss of dopaminergic inhibition to tonic PRL release (34–36)], which must be distinguished from a true prolactinoma. Under such circumstances, it is rare to see PRL levels >100 ng/ml, or at most 250 ng/ml. Consequently, large tumors (>2 cm in size) associated with PRL levels <250 ng/ml (certainly those <100 ng/ml) should be suspected of being nonfunctional when planning management strategies, and one would not expect such lesions to physically respond to chemical reductions of serum PRL.

Nonsecreting pituitary adenomas may be defined as those that demonstrate no *apparent* clinical or biochemical abnormality indicating hormone excess, although it must be recognized that the potential for the secretion of an as yet undetectable hormone or its precursor exists, or that an identified hormone may be synthesized in insufficient quantities to be detected by immunoperoxidase methods (37). Indeed, the term "nonfunctioning" has been considered a misnomer by some for this reason (38). To be distinguished from the true nonfunctioning tumors are those that secrete the α-subunit, common to all of the glycoprotein hormones. In these cases, the α-subunit may be detected immunohistochemically in tumor specimens and biochemically in the blood and urine but, because it possesses no biological activity, it is of no endocrinological consequence if secreted. However, the *exclusive* secretion of the α-subunit may be difficult to determine if each of the glycoprotein hormones has not been independently assayed. For example, TSH-secreting tumors may secrete excessive quantities of the α-subunit (39).

With nonfunctioning macroadenomas, varying amounts of hypopituitarism may be present, produced by compression of the gland by tumor or from interference with blood supply leading to infarction of the normal functioning gland. Reversal of hypopituitarism may be possible in some cases, illustrating that interruption of hypothalamic-portal circulation may occur without true necrosis of glandular tissue (40,41).

Therapy

The two objectives of the treatment of *all* pituitary tumors, regardless of secretory status, are (a) relief of signs and symptoms attributable to mass effect and (b) correction of endocrine abnormalities—hypo- or hypersecretion of adenohypophyseal hormones (42). When nonsecreting tumors are considered, hormonal hypersecretory syndromes may not be present but it is important to realize that continued growth of the lesion may precipitate hypopituitarism.

The success of medical therapy is predicated on the presence of any associated oversecretion of anterior pituitary hormones. Thus, in cases of nonfunctioning tumors, no pharmacological therapy is available. The primary mode of treatment considered in these tumors should therefore be *surgical*, with other options [radiotherapy (RT) or observation] only for patients whose underlying medical conditions preclude surgery (43). One exception is the asymptomatic elderly patient with a nonsecreting tumor, intact pituitary function, and no compromise of the visual system. A case can be made for monitoring the patient with routine clinical (visual field) and endocrine evaluations, with serial MRI or CT scanning performed at least yearly. These tumors may exhibit a benign course, without reaching symptomatic dimensions within the remaining life expectancy.

PRL-Secreting Adenomas

Clinical Manifestations and Diagnosis

PRL-secreting tumors are the most common kind of secretory pituitary tumor (44). Although these tumors are found pathologically at autopsy with equal frequency in men and women, they are clinically significantly more common in women. Hyperprolactinemia causes galactorrhea in women and hypogonadism, which presents as anovulatory infertility in the female and impotence in the male (45,46). Presumed abnormalities in pulsatile secretion of GHRH and gonadotropins precipitate a relative estrogen deficiency (47,48). This hypogonadal

state is associated with osteoporosis in women (49) and both cortical and trabecular osteopenia in men (50). In a personal series of some 392 PRL-secreting pituitary tumors operated on by one of the authors (M.H.W.), 321 (82%) were in female patients. The most common presenting symptom in this group was the development of secondary amenorrhea; only ~50% of those with amenorrhea had associated galactorrhea. Epidemiologically, ~5% of women with primary amenorrhea and 25% of women with secondary amenorrhea (other than those who are pregnant) harbor a PRL-secreting pituitary tumor as the cause of their clinical symptomatology. Because of this readily identifiable symptomatology, these patients generally present relatively early in the course of evolution of the tumors; this is unfortunately not true in the male population. Because the primary symptomatology of a PRL-secreting tumor in the male is usually a decrease in libido well before true impotence is observed, this is frequently ascribed to the "aging process" or "functional" causes. About two thirds of men with hyperprolactinemia due to a PRL-secreting tumor have a low serum testosterone level (51); this may be secondary to hyperprolactinemia per se or to mechanical compression of the adjacent normal pituitary gland. Thus, males often present at a more advanced age, and later in the course of their disease with chiasmal compression and visual compromise. For the same reasons, large tumors associated with hypothyroidism and adrenal insufficiency are more common in men (51).

The diagnosis is secured by radiographic evidence of a pituitary lesion with an elevation of serum PRL (52). As with other pituitary adenomas, high-field thin-section MRI appears to be the most sensitive imaging method for preoperative localization of the lesion. There exists a rough correlation between the size of the lesion radiographically and pathologically and the serum level of PRL. In addition, local invasion of the tumor into the adjacent venous cavernous sinuses is associated with a marked increase in serum PRL. The diagnosis of pathological prolactin excess should be based on serial blood measurements (53); PRL levels greater than five times the upper limit of normal are usually associated with a PRL-secreting pituitary tumor (54). In the endocrinological evaluation of the patient suspected of harboring a PRL-secreting tumor, as discussed previously, it must be appreciated that larger tumors of any endocrine basis may cause a mild to moderate hyperprolactinemia from stalk compression, which must be distinguished from a true prolactinoma.

A number of reports suggest that neither tumor size nor PRL levels change over a number of years in the majority of women with microprolactinomas (55,56). In fact, it has been observed that few microprolactinomas progress to macroadenomas (54). In contrast, macroadenomas, which for reasons already described frequently present in men, may behave in an aggressive manner (53). They may be associated with invasion of the cavernous sinuses and diffuse invasion of the base of the skull and may commonly extend to the suprasellar region (57). Hemorrhage or cyst formation within the tumor may also occur.

The absolute level of elevated PRL in a diagnosed pituitary adenoma is of great help in determining subsequent management because the ability to successfully extirpate the tumor is reduced with large and/or invasive lesions (discussed herein).

Indications for Therapy and Goals of Treatment

The introduction of an effective pharmacotherapy (bromocriptine) for PRL-secreting tumors demands a central role within the overall management strategy for these lesions. The efficacy of bromocriptine (a dopaminergic agonist) in reducing serum PRL, in addition to reducing tumor size and inhibiting further tumor growth, is well established (see herein). The central considerations related to treating such patients is the ability of the patient to tolerate the medication and the realization that the treatment must continue for the duration of the patient's life.

With PRL-secreting microadenomas, therapeutic options include medical or surgical management. In our series, 225 of 262 patients (86%) undergoing surgery for tumors <1 cm in size had normal (<20 ng/ml) postoperative PRL levels (ie, "chemical cure"). Operative mortality was zero and associated morbidity low. Strong consideration should be given to surgical intervention in patients harboring smaller tumors without significant hyperprolactinemia.

Very high levels of serum PRL (>1000 ng/ml) are usually indicative of an invasive tumor, an important consideration when contemplating the likelihood of surgical cure. For larger tumors, surgical chemical cures (serum PRL <20 ng/ml postoperatively) are much less frequent. Those tumors associated with PRL levels >200 ng/ml recur in >50% of

cases following surgery alone (45); recurrence of hyperprolactinemia after surgery for macroadenomas (with PRL levels >250 ng/ml) is >70% (38,45). In our personal series, only 63 of 130 (49%) of those patients with tumors >1 cm achieved chemical cure. Although no medical therapy results in cure of a PRL-secreting macroadenoma, only a minority of these patients remain free of their disease following surgery alone. Bromocriptine should therefore be considered as initial therapy for those patients in whom surgical resection resulting in chemical cure is deemed unlikely (58). It is our present practice to place *all* patients with large or invasive pituitary tumors with endocrinologically documented PRL secretion on a trial of bromocriptine initially and to monitor clinical status and radiographic appearance accordingly. All *solid* primary PRL-secreting tumors should respond to the medication, both clinically by a reduction in tumor size and by a reduction in PRL level. However, primary *cystic* tumors are much less likely to respond to pharmacotherapy (59).

The goals of treatment of prolactinomas include (a) reduction of the tumor mass, (b) correction of the hyperprolactinemic state, and (c) preservation of anterior pituitary function (45). The tenet of therapy should be absolute normalization of PRL levels because a prolonged hyperprolactinemic state may be associated with significant osteoporosis and infertility. Surgical resection of these lesions is indicated in those patients intolerant of the side effects of the medication, unable to afford the cost of the medication for a prolonged period of time, or in whom sustained tumor reduction is not effected. Subsequent to surgery, if hyperprolactinemia is persistent to some extent, the patient may be able to tolerate markedly reduced doses of bromocriptine to effect long-term control or one would consider the use of postoperative RT to bring the residual tumor under control.

After RT for prolactinomas, PRL levels fall slowly over many years, but rarely reach normal (45). Thus, these patients may benefit from adjuvant medical therapy with bromocriptine.

Pharmacotherapy with Dopaminergic Analogues

Physiology. Bromocriptine is a dopamine agonist that suppresses PRL production and release by the stimulation of dopamine receptors. This orally active dopamine agonist is a semisynthetic ergot alkaloid that was specifically developed as an inhibitor of PRL secretion. It directly stimulates neuronal and pituitary cell membrane dopamine receptors (60). A single dose of 2.5 mg results in suppression of serum PRL for ≤14 h (61). The biological effect, however, may persist >24 h in some patients (44).

Dose and mode of administration. Currently, bromocriptine is the only dopaminergic analogue that has been FDA-approved for the clinical treatment of hyperprolactinemia (45). It has proven safe and effective in 15 years of widespread use in the treatment of prolactinomas since its approval in 1978 (44). To avoid the occurrence of side effects when initiating therapy, a low dose of 1.25 mg should be administered at bedtime. Gradual increases in increments of 1.25 mg should be made every 3 to 4 days until the desired effect is reached (1). Most patients respond satisfactorily to a dose of 2.5 mg t.i.d. The medication should be taken with meals (44). In some patients with large tumors whose size does not decrease or whose PRL level is not suppressed by >80% of pretreatment levels with the above dose, much larger doses are required, up to 15 to 20 mg daily (44,45). However, in certain cases, the dose may be decreased after achievement of adequate suppression (44). In patients with macroprolactinomas treated initially with bromocriptine, if reduction in tumor size has not occurred ≤3 months, it is unlikely to occur, and medical therapy should be abandoned (45). In the bromocriptine-treated patient who responds but fails to normalize serum PRL and does not achieve restoration of gonadal function, a combined surgical and medical approach should be considered. After the surgical procedure, the hyperprolactinemia is often more responsive to medical therapy, requiring lower doses for control of PRL (45). Dopamine agonist therapy must be given chronically. In most patients, withdrawal of the drug results in a return of hyperprolactinemia and reexpansion of the tumor (62,63). Occasionally, patients with a microadenoma or an unidentifiable tumor do not have recurrence after discontinuation of therapy. In a patient with a microadenoma, bromocriptine can be discontinued every 2 years on a trial basis to determine the need for continued therapy (44,49).

Efficacy. Following adequate bromocriptine therapy, the PRL levels are usually lowered by >80% or normalized (45). The PRL-reducing response to therapy in patients with microadenomas and with macroadenomas is similar, with the exception that in the latter group, the time required for effective lowering of PRL is usually longer (44). In addition,

in >80% of patients, bromocriptine and other dopamine agonists are effective in reversing visual abnormalities and restoring gonadal and anterior pituitary functions (45,54). Most female patients begin menstruation ≤6 months of initiating therapy. The restoration of fertility in women with bromocriptine has been well documented (64).

In addition to reducing PRL secretion, bromocriptine is effective in decreasing tumor size (59, 65,66). The size reduction of the tumor may occur very rapidly, within days of initiation of therapy, and achieve dramatic decompression of the optic chiasm and resolution of headaches and other signs and symptoms of raised intracranial pressure (45). Some tumors are very responsive to bromocriptine and shrink >80% in ≤6 weeks of initiation of therapy (45). Although the vast majority of patients have a satisfactory biochemical and clinical response to medical therapy, there have been isolated case reports of lack of response or progression of disease during bromocriptine therapy (67–69). Close monitoring is therefore mandatory. In women, once hyperprolactinemia has been corrected and the menstrual cycle normalized, fertility is usually reestablished and the pregnancy rates are the same as those of normal women in the same age group (70,71). Although it is tempting to intuitively suggest that pretreatment with bromocriptine may shrink the tumor and facilitate surgical resection, no study has yet reported higher surgical cure rates after such preoperative treatment with bromocriptine (72,73).

Histological changes. Bromocriptine therapy of human prolactinomas for a period of 2 weeks has been shown to induce cell shrinkage and degenerative, necrotic, and fibrotic changes in the tumor; the secretory granules within a cell increase in number but not in volume (74). Others have demonstrated that the cytoplasmic and nuclear volumes are reduced. In the cytoplasm, the amount of rough endoplasmic reticulum and size of the Golgi apparatus are markedly reduced, and the cell changes from appearing highly active to quiescent. These changes are reversed after bromocriptine withdrawal (45).

Medical management and pregnancy. Pregnant women harboring microprolactinomas rarely develop complications related to tumor expansion; the reported risk ranges from only <0.5 to 1% (44,45). However, in pregnant women with macroprolactinomas, the situation is quite different; the risk of developing symptoms related to tumor enlargement such as headache, visual field disturbances, and ophthalmoplegia is ~15%, and that of developing asymptomatic tumor enlargement 9% (75). These complications appear to occur with equal frequency during all trimesters (70). Therefore, measures to reduce tumor size such as surgery and radiation are recommended prior to conception in female patients harboring macroadenomas who desire to become pregnant. In the event of significant tumor enlargement during pregnancy, bromocriptine has been shown to be safe and effective (76–78). Its administration during pregnancy has not increased the risk of congenital anomalies, spontaneous abortion, or multiple births (79,80). Motor and psychological development of children born to women treated with bromocriptine during pregnancy were normal (80).

If a pregnancy is planned by a patient on bromocriptine therapy, a coordinated schedule of follow-up must be observed by the patient, endocrinologist, and neurosurgeon. It is currently recommended that a woman with a prolactinoma, regardless of tumor size, who wishes to become pregnant while on bromocriptine therapy use mechanical contraceptive precautions for 3 months. During this period, she should undergo complete endocrine, neuroradiologic, and neuroophthalmologic evaluations. After achieving three regular menstrual cycles, she should discontinue the contraceptive precautions. Pregnancy should be suspected when the menses are 2 days overdue, and at that time a serum β-human chorionic gonadotropin level should be measured. Once pregnancy is confirmed, the bromocriptine should be immediately discontinued. The patient would then be followed closely for signs and symptoms of tumor expansion. Should visual field abnormalities develop, bromocriptine therapy would be indicated as the clinical situation warrants (44). After termination of pregnancy, headaches and visual field defects acquired due to tumor expansion resolve as the tumor becomes smaller in all cases.

Side effects. Significant side effects of bromocriptine include malaise, nausea, vomiting, and postural hypotension. Less commonly, headache, abdominal cramps, constipation, nasal congestion, and depression have been described. Hallucinations have been reported in 1.3% of patients (81) and, rarely, cold-induced vasospasm most pronounced in the digits may occur (82). A rare complication in patients with large prolactinomas is the development of a cerebrospinal (CSF) fluid leak during treatment, caused by shrinkage of the tumor (49). In

women, galactorrhea may persist even though PRL is lowered to the normal range (83). It has been reported that if bromocriptine is given for months, the tumor may become fibrous in consistency, which may cause difficulty with surgical resection (65). This has not been our personal experience.

GH-Secreting Adenomas

Acromegaly and *gigantism* are the result of oversecretion of GH into the somatic circulation. Collectively, they are second in frequency to hyperprolactinemia as pituitary hypersecretory syndromes. They are almost always caused by a somatotroph (i.e., GH-secreting) adenoma of the pituitary (>99% of cases) as opposed to somatotroph hyperplasia from excess secretion of ectopic GHRH (82). The majority of these pituitary tumors exhibit a moderate growth rate and often present as macroadenomas with extrasellar extension and focal destruction (84,85) [85 to 90% of patients present with macroadenomas and 10 to 15% with microadenomas (82)].

Younger patients with acromegaly often harbor larger and more rapidly growing tumors (86). Acromegalic tumors may contain and also secrete PRL or the α-subunit (common to all the glycoprotein adenohypophyseal hormones) and, rarely, TSH in addition to GH (84). Most patients with large tumors have mixed GH and PRL hypersecretion (87), which results in concomitant hyperprolactinemia in 20 to 40% of patients (84,86). PRL is most often secreted from a tumor containing a mixed population of somatotroph and lactotroph cells (an acidophilic stem cell tumor) but occasionally from a bipotential mammosomatotroph adenoma (85). In patients harboring mammosomatotroph adenomas, the two hormones by definition are present within the same cell and/or the same secretory granule and are usually secreted in a similar dynamic pattern (86).

The total amount of GH secreted in a 24-h period is variable among patients and depends on cell activity but roughly correlates with the size of the tumor (88). GH oversecretion results in elevated plasma IGF-1 levels (84) that are fairly stable and reflect the integrated, pulsatile 24-h secretion of GH. As GH levels increase, IGF-1 rises linearly until GH reaches ~20 μg/L, after which the IGF-1 level plateaus. As a corollary, to achieve any measure of successful treatment, GH must decrease to a level <20 μg/L for IGF-1 levels to drop or clinical improvement to occur (82). However, there is a poor correlation between plasma GH levels and clinical manifestations of acromegaly, presumably because of variable responsiveness of peripheral tissues to GH excess (84).

Clinical Manifestations and Diagnosis

The clinical manifestations of excess secretion of GH are dependent on the age of the patient. If the excess secretion occurs in childhood or adolescence before the epiphyses of long bones have fused, the result is *gigantism*. Such individuals may attain great height (often >7 ft) if the disease progresses unchecked. After fusion of the epiphyses, excess GH produces the syndrome of *acromegaly* in adults, with soft tissue and bony enlargement in characteristic locations. Clinical manifestations of these soft tissue changes include coarsening of facial features, laryngeal enlargement, goiter, thick heel pads, acanthosis nigricans, cardiomegaly, and hepatomegaly. Bony changes are extensive, producing facial prognathism, enlargement of the mandible with increased spacing between the teeth, and bony enlargements of hands and feet. Soft tissue and bony changes may produce compressive neuropathies and arthropathies. Metabolic manifestations include hypertension, diabetes mellitus, and goiter, and, commonly, hyperhidrosis. Deficiencies in ACTH and TSH are found in >10 to 20% of patients. Hypogonadism occurs in 30 to 40% of patients but may be attributable to associated hyperprolactinemia (84) and may result in osteoporosis. Acromegaly affects men and women with approximately equal frequency.

The diagnosis is made by assessing GH secretion. A basal fasting GH level >10 ng/ml is present in 90% of acromegalics. However, because GH is secreted in several peaks throughout the day, a single fasting level may fail to demonstrate an elevated level in some patients. The suspected diagnosis is therefore confirmed by the glucose suppression test. In the acromegalic, an oral administration of 100 g of glucose fails to suppress the serum GH level to <2 μg/L at 60 min. The measurement of serum IGF-1 levels are elevated in acromegalics and prove to be a more reliable measure of the disease and its response to treatment. Radiographic imaging (MRI and/or CT) demonstrates the presence of a pituitary adenoma in >90% of patients with endocrinologically documented acromegaly.

Indications for Therapy and Goals of Treatment

Excess secretion of GH should be considered a malignant endocrinopathy that may result in life-threatening medical complications and thus should be treated aggressively once diagnosed. The goals of therapy in management of a GH-secreting pituitary adenoma include (a) resolution of tumor mass effect, (b) restoration of normal GH physiology (absolute normalization of GH and IGF-1 levels), and (c) replacement of any associated hormone deficiencies. Many authors now believe that criteria for successful therapy (chemical cure) include a 24-h integrated GH concentration ≤ 2.5 μg/L together with normalization of the circulating IGF-1 level (85,89).

Microadenomas

In the patient harboring a GH-secreting microadenoma who is sufficiently medically stable to undergo surgery, surgical resection should be considered the optimal first line of management. The transsphenoidal approach is certainly the approach of choice to these lesions, but the transnasal dissection in the acromegalic patient with associated soft tissue and bony changes may present an added challenge for the surgeon. However, in our personal experience, this has never been a limiting factor in the use of the transsphenoidal approach. Such tumors may be cured by chemical criteria in the majority of cases. In our personal series, 74% of patients with microadenomas undergoing transsphenoidal resection achieved normal postoperative IGF-1 levels, and 76% achieved postoperative GH levels <5 μg/L. Postoperative persistent elevation of GH or IGF-1 levels are an indication for pharmacotherapy or RT (discussed herein).

Macroadenomas

The patient harboring a GH-secreting macroadenoma poses a more difficult management dilemma. Certainly the likelihood of cure in these tumors is low in cases of large tumors with frank cavernous sinus invasion, and pharmacotherapy or RT should be considered integral components in the overall management plan. In these cases, initial pharmacotherapy may be indicated; however, surgical resection may be helpful in decreasing tumor load to effect an absolute normalization of IGF-1 levels by pharmacotherapy (90).

Pharmacotherapy

Pharmacotherapy should be considered in (a) patients in whom surgery is contraindicated; (b) patients whose GH and IGF-1 levels are still elevated after surgery, as an alternative for RT at this stage; or (c) patients with elevated GH and IGF-1 levels after surgery and RT (82). Medical therapy may be administered in conjunction with RT to provide interim GH suppression while awaiting the beneficial effects of the radiation.

Somatostatin Analogues

Physiology. Native somatostatin is believed to control GH secretion by suppression of GH release from the pituitary gland and GHRH from the hypothalamus (91). There is at present only one FDA-approved analogue appropriate for clinical use—octreotide (Sandostatin, Sandoz, East Hanover, NJ, U.S.A.; previously designated SMS 201-995) (92). Octreotide contains the active sequence of somatostatin. Octreotide appears to control GH secretion by suppression of GH release from the pituitary gland and by suppression of GHRH from the hypothalamus (91). In comparison to the native hormone, it has enhanced binding affinity to the somatostatin receptor and a prolonged half-life of 110 min after s.c. injection of a 50- to 100-μg dose, providing an overall duration of effect of 6 to 8 h (93). A single injection of octreotide produces a decrease in GH levels within 30 to 60 min, with maximum suppression of GH levels occurring in 2 to 4 h (94). Analogues currently under investigation have greater biologic potency than octreotide and are more specific for the pituitary gland (85).

Tumor somatostatin receptor status. Large numbers of specific somatostatin-binding sites in human GH-secreting pituitary adenomas have been demonstrated (95–97). There appears to be heterogeneity with regard to the number of somatostatin receptors between tumors and in their distribution within a particular tumor. Most tumors contain somatostatin receptors in densities comparable to those in normal somatotrophs (97) and respond normally to somatostatin (98). However, 10 to 30% of GH-secreting tumors have reduced numbers of somatostatin receptors; patients with such tumors ex-

hibit diminished in vivo responses to octreotide (97).

Dose and mode of administration. The usual initial dose is 100 μg s.c. every 8 h, and this dose should be increased until adequate suppression is achieved. In acromegalics treated with octreotide, a close correlation has been found between the mean 24-h GH levels and IGF-1 levels before and during therapy (99–102). Therefore, regular IGF-1 measurements on an outpatient basis enable optimization of the daily dose and number of octreotide injections needed for each individual patient (100,102). The majority of patients achieve control with 300 to 600 μg per day (94). In a recent national survey, doses of 750 μg per day resulted in increased frequency of tumor shrinkage without adding any biochemical or clinical benefit (103). Over a 6-month period, the size of the pituitary tumor was reduced in 34% of patients receiving this latter dose versus 17% of patients receiving 300 μg per day. At present, the maximum recommended dosage is 1500 μg per day (85). As many as 50% of patients can be maintained on a twice daily regimen (104), but some patients may achieve better control by administering the same daily dose every 6 h instead (85). In this regard, continuous s.c. pump infusion of 100 to 600 μg per day has been shown to provide superior and more stable suppression of mean 24-h GH levels (105).

Efficacy. Seventy-five to 90% of acromegalic patients experience biochemical, clinical, and metabolic improvement with octreotide therapy. Clinical improvement may be heralded by disappearance or amelioration of excessive sweating, headaches, paresthesia, soft tissue swelling, and joint pain and improvement of nerve entrapment symptoms, together with a general sense of well-being (85,103). Immediate and prolonged relief of headaches is experienced in some patients with acromegaly, generally those with evidence of suprasellar tumor extension (106). Visual field improvement has been noted in many without demonstrable change in tumor size (described herein) (85). In some patients, dose- and time-related symptoms indicative of drug dependency occur (107) and may be mediated by the binding of octreotide to the opioid μ-receptor (85).

Effective decreases of GH and IGF-1 levels occur in 30 to 53% and in 40 to 68% of patients, respectively, according to various studies (85,93,94,103, 108,109). In most patients, IGF-1 levels fall ≤1 week of the start of treatment and tend to normalize in 37 to 81% of cases with continued therapy (103,104,110–112). GH and IGF-1 levels have been shown to continue to decrease with long-term treatment of 1.5 to 2 years when compared to levels at 6 to 12 months (113). Long-term responsiveness can be predicted by the acute GH-suppression effect of a single test injection of 50 μg of octreotide. The mean hourly GH level from 2 to 6 h after drug injection or any time during s.c. infusion are also useful predictors of efficacy (85). Plasma PRL levels in patients with mixed GH-PRL-containing tumors have been shown to be suppressed by octreotide in about one half of cases (113). Elevated concentrations of the α-subunit, which can be found in ~35% of acromegalic patients (115), respond to octreotide in a similar fashion to the changes in GH level (94).

Preoperative treatment with octreotide causes the tumor to become soft in consistency and to exhibit a grayish-red color at surgery (116). Several neurosurgical groups have concluded that pretreatment with octreotide with softening of the adenoma has facilitated surgical resection (116,117). Long-term octreotide therapy produces a slight decrease in pituitary tumor size in ~20 to 50% of acromegalic patients (100,101,103,118). Complete tumor shrinkage has been reported in isolated cases (119). Tumor size may increase soon after stopping the drug (120), but in occasional patients, a period off the drug may subsequently permit comparable control to be achieved with a lower dose. This phenomenon is possibly explained by a reversal of somatostatin receptor down-regulation (85).

Histological changes. Shrinkage of adenomas during octreotide therapy might reflect a decrease in the size of individual tumor cells (94). Electron microscopy of adenomas pretreated with octreotide revealed small necrotic cells and a greater number of macrophages; normal pituitary cells showed an accumulation of lipoprotein and secretory granules (121). These morphological findings were primarily consistent with chronic suppression of GH release.

Side effects. Though the drug is generally well tolerated, several side effects have been reported. Within the first few days of administration, a transient decrease in gastrointestinal motility and slowed absorption occur in most patients. The patient may experience transient abdominal pains and bloating. Steatorrhea, presumably due to a reduction in pancreatic exocrine secretion (104), occurs less frequently but may persist with long-term therapy. Treatment with pancreatic enzymes, if necessary, is usually effective (82). Nutritional deficiency has not been reported. Toxic hepatitis has occurred

very infrequently. Inhibition of insulin secretion can lead to hyperglycemia, though the concomitant improvement in glucose tolerance as a consequence of a decrease in GH secretion is generally sufficient to prevent this. Though somatostatin inhibits TSH secretion, hypothyroidism has not been reported during long-term octreotide therapy (100,101,110). The side effect of greatest concern is cholelithiasis due to suppression of cholecystokinin secretion and a resulting decrease in bile flow. Because the incidence of gallstone formation in patients on long-term octreotide is 40 to 50% (89,122), all patients should be regularly screened for gallstone development during treatment (104). No allergic reactions related to octreotide have been reported, although antibodies to octreotide have been detected in one patient (87). Tachyphylaxis or desensitization have not been observed during long-term treatment (94). Although the injections are often painful, this may be minimized by slow injection of the drug (82).

Dopaminergic Analogues

Physiology. Dopamine agonists stimulate GH secretion from normal subjects through a CNS-mediated mechanism that increases GHRH secretion (123) and possibly through the regulation of somatostatin secretion (85). In contrast, in acromegalic patients, the agonists *suppress* GH secretion in at least half of cases (124) through a PRL-dependent D_2 receptor mechanism (53). Dopamine agonists are primarily effective in GH-secreting tumors that also secrete PRL (85). Unfortunately, many acromegalic tumors contain few or no D_2 receptors, which is reflected by a poor clinical response to these drugs.

Dose and mode of administration. All the currently available agents are members of the ergoline family of compounds. As stated previously, bromocriptine (Parlodel, Sandoz, East Hanover, NJ, U.S.A.) is available for use in the United States. Initiation of bromocriptine therapy is as described in the previous section for use in PRL-secreting adenomas. Up to 20 to 30 mg bromocriptine per day has been used to obtain maximum benefit, a dose that has been frequently associated with side effects (82,85).

Therapeutic effects. Amelioration of signs and symptoms of GH excess occur in 70% of treated acromegalic patients although GH levels are reduced to $\leq$10 ng/ml in only 50% and to $\leq$5 ng/ml in only 20% of these patients (85). Only 8% of patients achieve normal IGF-1 levels, which is the only reliable parameter for assessing overall normalcy of pulsatile GH secretion (82). Less favorable results are seen with larger tumors and if initial GH levels are >50 ng/ml (53). Tumor shrinkage is uncommon, occurring in only 10 to 15% of patients (85,125).

The only known factor predicting responsiveness to dopaminergic agonists is coexistence of PRL hypersecretion. Even in such patients, it is not unusual to achieve total suppression of prolactin secretion with only partial or no suppression of GH (85). A single test dose of bromocriptine (2.5 mg po) followed by hourly plasma GH levels for 4 to 6 h may be used to assess therapeutic efficacy. Caution should be observed during this test because side effects may occur following administration of this dose.

Histological changes. At a morphological level, bromocriptine produces almost no change in human GH-secreting adenomas, except for an increase in the stromal tissue volume with occasional occurrence of vacuolation and single-cell necrosis (74).

Side effects. Commonly occurring side effects of bromocriptine therapy have been discussed previously in the PRL-secreting adenoma section.

Combined Use of Bromocriptine and Octreotide

Few patients who do not respond to either octreotide or to bromocriptine alone respond to the combination of octreotide and bromocriptine (94, 113,126,127).

ACTH-Secreting Adenomas

Clinical Manifestations and Diagnosis

Cushing's disease is the result of hypersecretion of ACTH by the pituitary. ACTH-secreting tumors exist in >90% of such patients, with diffuse corticotrope hyperplasia from hypersecretion of CRH as the cause of excess ACTH secretion in the remainder. The disease affects women ~8 times more frequently than men.

Clinical manifestations of the disease include (a) those due to glucocorticoid excess: central obesity, "moon" facies, dorsocervical and supraclavicular fat pads, proximal muscle wasting, thin skin with ecchymoses and violaceous striae, cataracts, osteoporosis, amenorrhea, diabetes mellitus, hypertension, hypercalcuria (due to bone resorption),

growth retardation in children, and immunosuppression with fungal infections; and (b) those due to peripheral androgen excess: hirsutism and acne (virilization is unusual). Peripheral androgen and cortisol excess may cause hypogonadism by increasing the negative feedback to the pituitary and hypothalamus.

The diagnosis of Cushing's disease is confirmed by (a) increased basal plasma cortisol levels and urinary excretion of free cortisol (two consecutive basal 24-h urine collections); (b) inappropriately high plasm ACTH concentrations (i.e., within or above the normal range); and (c) relative resistance to glucocorticoid negative feedback-inhibition. This relative resistance is shown by (a) low-dose dexamethasone suppression test (overnight 1 mg dexamethasone screening test or the standard 2-day test of 0.5 mg q6h for 2 days) that distinguishes Cushing's syndrome of any cause from normal cortisol secretion (plasma cortisol and ACTH levels should be suppressed to <140 nmol/L and 4.4 pmol/L, respectively); and (b) high-dose dexamethasone suppression test (overnight 8 mg dexamethasone test or standard 2-day test of 2 mg q6h for 2 days). Any degree of reproducible suppression that is greater than the daily variation and assay error is indicative of Cushing's disease. ACTH secretion is already suppressed in patients with either adrenal tumors or ectopic ACTH syndrome.

Cushing's disease may also be differentiated from ectopic ACTH secretion by performing (a) the CRH test (in Cushing's disease, ACTH secretion responds to CRH) and (b) a metyrapone test, in which case there is an increase in plasma ACTH level and 11-deoxycortisol level (>5 μg/dl) in the setting of an undetectable plasma cortisol concentration. The ectopic ACTH-producing tumor does not respond to CRH and demonstrates a subnormal response to metyrapone. Petrosal venous sampling may be indicated to localize a pituitary ACTH-secreting adenoma undetected by CT or MRI studies. With this technique, a pituitary ACTH-producing tumor is identified when a gradient is noted between the petrosal vein and the peripheral blood (128).

Therapy

Fortunately, most patients with Cushing's disease harbor microadenomas that lend themselves to complete surgical resection (129). Our experience with these microadenomas has been gratifying; in those patients with Cushing's disease harboring microadenomas, the series has demonstrated a 91% chemical cure rate. On the other hand, patients with Cushing's disease who harbor macroadenomas present a serious problem. These tumors are frequently invasive into adjacent dura and bone and consequently defy chemical cure by surgical means alone. If elevated ACTH levels persist after radical surgical resection and no residual intrasellar tumor is defined by imaging studies, we are currently exploring stereotactic radiosurgery as a method to eradicate residual sellar and parasellar invasion while sparing adjacent structures (as opposed to standard external beam RT; description herein).

Adults respond to conventional external beam RT in only 40% of cases and do so over a period of 12 to 18 months (128). For the 60% of patients who do not respond, medical treatment is indicated. In this latter group, RT has the beneficial effect of protecting the patient from developing Nelson's syndrome at a later date. The first line of medical therapy consists of an adrenolytic agent, mitotane, for a period of 6 to 9 months, with the goal of suppressing cortisol secretion. Mitotane is initiated at a dose of 0.5 g per day and increased to 4 g per day, half the dose being administered at bedtime to alleviate side effects. Dexamethasone replacement therapy should be started to avoid adrenal insufficiency. Mineralocorticoid replacement is usually not required. Side effects include nausea, vomiting, rash, leukopenia, ataxia, gynecomastia, and arthralgias. Twenty percent of patients do not respond to mitotane and require therapy with an adrenal enzyme inhibitor that usually controls the disease. These agents include aminoglutethimide at a dose of 250 mg b.i.d. or t.i.d. This drug increases dexamethasone metabolism, and therefore replacement with hydrocortisone is required. Aldosterone production will be inhibited, and replacement therapy with a mineralocorticoid such as fludrocortisone is necessary. Side effects of this medication include a transient pruritic rash, hypothyroidism, goiter, and somnolence when dosages >1 g per day are administered. The second adrenal enzyme inhibitor available is metyrapone, which only partially decreases serum cortisol levels. This medication is indicated when cortisol elevation is mild or following RT while waiting for full clinical effect. The dose required is ~2 to 4 g per day in divided doses. Side effects include nausea, headaches, sedation, and rash. Ketoconazole is a third enzyme inhibitor that also inhibits ACTH. The usual dose necessary is 200 to 400 mg po b.i.d. or t.i.d. Side effects include nau-

sea, vomiting, headache, impotence, gynecomastia, and reversible hepatotoxicity. Metapyrone and aminoglutethimide are often used in combination at lower dosages to reduce side effects.

In those patients in whom surgical therapy, RT, or medical therapy has been unsuccessful, adrenalectomy is indicated (128).

Other Secreting Pituitary Adenomas

Tumors of the pituitary causing oversecretion of TSH or gonadotrophs have been described but are much less common than those previously mentioned (Table 2). In patients harboring TSH-secreting adenomas, the TSH level is <10 mU/L in one third of cases (4). These cases can be differentiated from other sources of hyperthyroidism by the presence of an α-subunit:TSH ratio >1. Gonadotroph adenomas usually present in middle-aged men with normal sexual function, headache, and visual changes. Hypersecretion of intact FSH is the most common anomaly; inappropriately normal LH levels in the presence of a low testosterone value may also occur. This LH hormone is biologically inactive. Hypersecretion of intact LH by some tumors causes elevation of serum testosterone levels. Elevated serum α-subunit concentrations may also be detected. In ~50% of patients with gonadotropic tumors, administration of exogenous TRH provokes inappropriate elevations of serum LH and FSH. The TRH test may therefore be of diagnostic value.

The treatment of these lesions is surgical, with RT reserved for those patients who are not surgical candidates or in whom total resection is not achieved. Reports of octreotide lowering serum TSH concentration in patients harboring TSH-secreting tumors have been described. If hyperthyroidism persists despite surgery and RT, treatment with antithyroid drugs may be necessary.

SURGERY FOR PITUITARY ADENOMAS

Historical Background

Although Marie correctly ascribed the clinical syndrome of acromegaly to the presence of a pituitary adenoma as early as 1889, it was not until 1893 that Caton and Paul recorded the first attempt at surgical resection of a pituitary tumor (130). Their attempt at utilization of a two-stage lateral subtemporal procedure as suggested by Sir Victor Horsley (131) was unsuccessful; the patient died before this effort could be completed. Subsequently, Horsley himself, utilizing a lateral middle fossa approach, reported successful surgical resections in 8 of 10 pituitary tumors operated on between 1904 and 1906. Krause in 1905 introduced the frontal transcranial approach to the sella; this technique has provided the basis for a majority of subsequent variations of transcranial approaches (132).

These basic approaches were modified and augmented by a number of the giants of neurosurgical development in the early part of the twentieth century. Modifications of these approaches described by Frazier, Dandy, Heuer, and Cushing, primarily favored the direct intradural approach to the sella and its contents. With the profound influence of these individuals, it could be recognized by the 1930s that most neurosurgical approaches to the pituitary centered about a transcranial intradural technique even though some neurosurgeons continued to utilize an extradural approach. Heuer (133) advocated a lateral anterior fossa approach using the landmarks provided by the sphenoid ridge. This approach seemed to be the shortest distance between the inner table of the skull and the sella. Frazier (134), on the other hand, described a frontal transcranial approach beginning at the midpoint between the midline and the lateral sphenoid wing. Cushing, finally, preferred a direct midline approach (135). The dominant neurosurgical teaching during the 1930s and 1940s continued to focus on a transcranial approach to the pituitary; this technique was further refined and promulgated by the extensive experiences of Olivecrona (136) and Ray (137) during the 1950s. These major figures of international neurosurgery promulgated the utilization of a transfrontal intradural approach to the pituitary during the course of developing an extensive experience with hypophyseal ablation that had become a major adjunct in the management of metastatic breast and prostate carcinoma as well as diabetic retinopathy. Ray personally performed >1,000 procedures on the pituitary and emphasized the need for a properly placed low bone flap to minimize brain retraction in gaining access to the sella and parasellar areas.

The earliest attempts at transcranial approaches to the pituitary at the turn of the century and shortly thereafter, however, resulted in a mortality that was generally considered prohibitive. Horsley, in the small series of 10 cases referred to previously, experienced a 20% mortality, certainly unacceptable

by modern standards but indeed significantly better than the experiences of his colleagues who reported mortalities ranging from 50 to 80%. It should be recognized that this extraordinary incidence of mortality was generally accepted in the efforts of developing intracranial surgery at that time.

As a consequence of these earlier experiences, attempts were continually made to modify surgical techniques and adjuvant management in an effort to make the surgical approach to the pituitary a more reasonable option for both surgeon and patient. In this light, Schloffer, a rhinologist from Innsbruck, Austria, recommended utilization of a transsphenoidal route as an alternative and presumably safer approach to the sella turcica and its contents. Indeed, in 1907, he reported the first successful removal of a pituitary tumor using the transsphenoidal approach (138). The technique of sphenoid sinus exposure subsequently underwent a number of modifications by interested surgeons, and the culmination was Halstead's description in 1910 of the sublabial gingival incision for the initial stage of sphenoid sinus exposure. After initial disappointments at transcranial efforts, Cushing himself embraced the transsphenoidal approach. He described a technique that combined a number of suggestions made by previous authors and employed the sublabial incision described by Halstead (Fig. 1). Cushing also adopted the technique of submucous dissection of the nasal septum promulgated by Eiselberg and Kocher and employed the headlight described by Kanavel to enable better visualization in the depths of the operative field during surgery. Utilizing the transnasal/transsphenoidal approach during the 15-year period from 1910 to 1925, Cushing operated on some 231 pituitary tumors with a reported mortality of 5.6%. This certainly represented the best efforts at surgical exposure and access to the pituitary at the time (139).

Mortality and morbidity from use of the transsphenoidal approach related primarily to infection that was frequently associated with postoperative CSF rhinorrhea; on the other hand, hemorrhage and postoperative edema underlay the excessive mortality and morbidity experienced with transcranial approaches. However, as Cushing developed increasing expertise and confidence in transcranial surgery, he again began to utilize the transcranial approach to the pituitary. As he gained experience, Cushing finally reduced his mortality with the transcranial approach to 4.5%, essentially eliminating any significant differential between the mortalities experienced with transsphenoidal and transcranial approaches. It was his opinion that visual recovery was more complete following direct decompression of the optic nerves and chiasm which may certainly have been the case in those early times. In addition, Cushing recognized that the transfrontal approach allowed more extensive resection of those suprasellar tumors complicated by significant lateral extension (139). Obviously, Dr. Cushing's intense interest in intracranial surgery must have contributed to his pursuit and development of transcranial approaches to the pituitary. Other distinguished surgeons, however, such as Hirsch (140) and Hamlin (141), continued to use the transsphenoidal approach with reports of excellent results. It is reported that Dr. Cushing, on the occasion of his 70th birthday, remarked that the transsphenoidal approach, because of its many advantages, would probably return despite the liabilities he perceived.

Because of the dominance of Cushing in the evolution of neurosurgery in the United States and the outstanding results that he reported, the utilization of transsphenoidal operations on the pituitary diminished profoundly during this period until Norman Dott of Edinburgh, a student of Cushing, refocused attention on this technique (142). In turn, Dott reportedly introduced Guiot of France (143) to the technique of transsphenoidal approach to the pituitary, and Guiot subsequently influenced the extensive development of this technique by Jules Hardy of Montreal (144). Accumulating an extensive experience in transsphenoidal microsurgery, these individuals significantly altered and redefined the indications and risks related to the transsphenoidal resection of hypophyseal and parahypophyseal tumors. In addition, refinement of the techniques for closure of the opening between the sphenoid sinus and the intracranial compartment has resulted in a profound decrease in the mortality and morbidity associated with this procedure.

Radical operative procedures involving the hypophysis carried a prohibitive complication rate before the development of commercially available corticosteroids in the early 1950s. Replacement of these agents in patients who are rendered hypopituitary either by the development of a tumor of other mass or as a consequence of surgical extraction of such lesions is essential for successful surgical intercession; commercial availability of the corticoids has truly revolutionized postoperative morbidity and mortality in these efforts.

Preoperative Evaluation

Any lesion proximal to the pituitary or hypothalamus requires adequate endocrine evaluation preoperatively to minimize the potential for an intraoperative or postoperative catastrophe because of inadequate pituitary reserve. The two most important of these evaluations are cortisol and thyroid levels. Because of the universal use of perioperative glucocorticoids in surgery involving this area, the risk of intraoperative hypocortisolemia is generally not a major factor. However, preexistent hypothyroidism may manifest acutely during the early postoperative period, underlining the need for adequate preoperative assessment. In patients with associated hypothyroidism, reestablishment requires ~1 week of treatment before any elective surgical procedure. In the event of concomitant hypocortisolism, to avoid precipitating an adrenal crisis, the cortisol deficiency must be treated before initiating thyroid hormone therapy. For this reason, complete endocrine evaluation is performed on all patients suspected of harboring a pituitary lesion. Of course, normalcy preoperatively does not guarantee such a state postoperatively, but an understanding of preoperative function may indicate those patients in whom a risk of this occurrence should be considered in the perioperative period.

An assessment of electrolyte status is also important to define the patient with marginal DI (145–148) who may not comment on the long-standing urinary frequency from an historical perspective.

Transsphenoidal Approach

As noted previously, the transnasal transsphenoidal approach is currently considered the procedure of choice for surgical access to sellar lesions. The increase in popularity of this technique may in part also be attributed to the well-recognized inadequacy of the subfrontal approach to remove the intrasellar component of the tumor (149–154). Moreover, several reports exist of favorable results in the management of visual disturbances from macroadenomas using the transsphenoidal route, establishing this as the approach of choice for the surgical management of most pituitary tumors, regardless of size (Fig. 2) (150,155). Our assessment of >200 patients who presented with visual loss from among our first 1,000 pituitary patients operated on via the transnasal transsphenoidal route yielded evidence of improved vision in 81%, unchanged vision in 16%, and worsening of vision in 3%. These results are similar to other large series that have been reported concerning the efficacy of the transsphenoidal approach to suprasellar tumors, and these results certainly equal or exceed the results of large series of subfrontal explorations for visual loss. In addition, there exists clear documentation of the potential for *improvement in pituitary function* after transsphenoidal adenomectomy with careful preservation of normal gland in cases with preexisting hypopituitarism (40,41). The efficacy of transsphenoidal surgery in selected patients with microadenomas has been established, with some reports of >90% tumor control (129,156). In series including larger tumors, however, a less optimistic 50 to 85% tumor control is expected with surgery alone (150, 157,158).

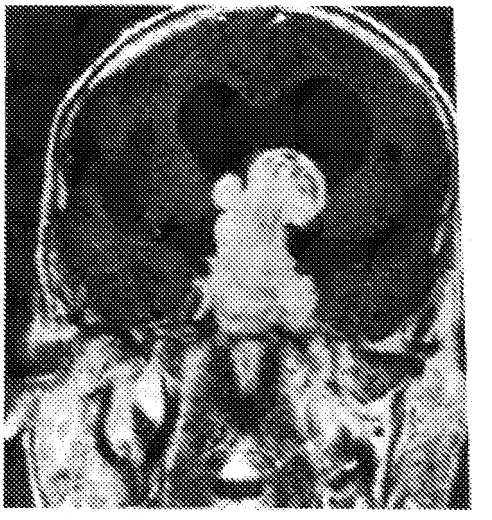

FIG. 2. Choice of surgical approach: transsphenoidal versus transcranial? This T1-weighted magnetic resonance image with gadolinium enhancement demonstrates a large macroadenoma that shows mostly vertical growth with no significant middle fossa extension. For this reason, a primary transsphenoidal approach was chosen with adequate decompression of the visual apparatus.

Transsphenoidal microsurgery for both large and small adenomas done by experienced surgeons has acceptable mortality and morbidity (159). Of 2,606 microadenomas and 2,677 macroadenomas reported in an international survey by Zervas (66), the death rate was 0.27 and 0.86%, respectively. Direct injury to the hypothalamus seemed to be the major cause of surgical death, with delayed mortality attributed to CSF leaks and their attendant septic complications, or by vascular injury. Operative morbidity includes persistent or permanent DI, the incidence ranging from 1.8% permanent DI in one

large series (160) to a 17% incidence immediately postoperatively with large adenomas (155). Postoperative CSF fistulas range from 1 to 4.4% among different series, depending on the size of the lesion and follow-up time, but occur disproportionately with larger lesions (66,161–163). Other major morbidity (stroke, visual loss, vascular injury, meningitis, CSF rhinorrhea, cranial nerve palsy) is encountered in 3.5%, and minor morbidity (bleeding, nasal or sinus problems, DI, syndrome of inappropriate antidiuretic hormone, transient cranial nerve paresis, transient psychosis) occurs in another 3.5% of patients (164). As put forth by all of these authors, complications amount to a relatively small percentage of the overall surgical experience, emphasizing the relative safety of the procedure.

Although it is the procedure of choice for the majority of pituitary tumors, the rare relative contraindications to the transsphenoidal approach include (a) extensive lateral tumor herniating into the middle fossa with minimal midline mass (these cases *may* require a primary or secondary transcranial procedure to remove tumor inaccessible by a midline approach); (b) midline projecting ectatic carotid arteries that are at risk of injury using a transsphenoidal approach (Fig. 3); and (c) acute sinusitis, that may delay the procedure for treatment of the infection. Previous rhinoplasty or submucous resection may increase the difficulty developing the dissection planes, but these can invariably be established. Thus these factors should not themselves constitute contraindication of the transnasal approach.

A detailed description of the transnasal transsphenoidal procedure performed at our institution has been published (162) and is reviewed in Fig. 4–8. Adequate bony removal is essential to enable complete sellar access. The location of the carotid arteries on the coronal MRI should be noted; this information is valuable when opening the dura at the lateral margins of the sella. Characteristically, these tumors are soft and friable and at surgery may herniate down through the diaphragma sellae after evacuation of the intrasellar component; this may be facilitated by the anesthetist performing a Valsalva maneuver intraoperatively. Other techniques to promote tumor descent include the infusion of air or saline through a previously placed cisternal or lumbar catheter (38,165). A pure suprasellar tumor, or one that requires suprasellar access, may be approached, if necessary, by carrying the bony resection anterior over the tuberculum sellae with exposure of the dura mater lying anterior

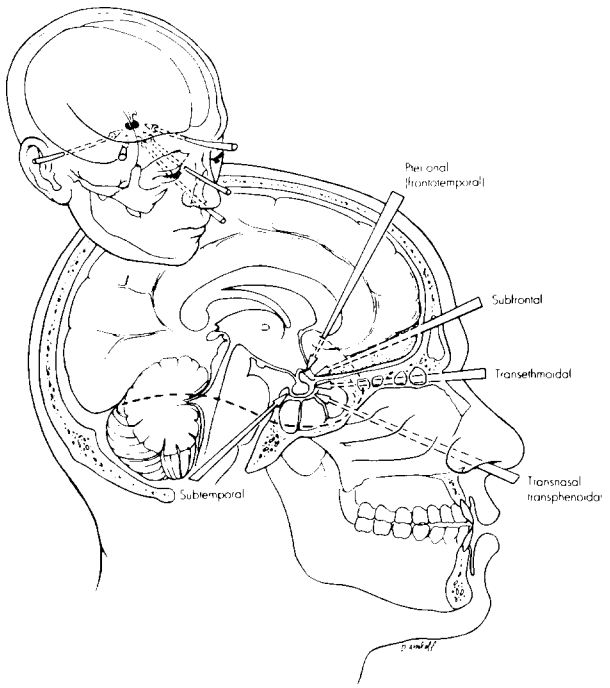

FIG. 3. Surgical approaches to the sella and suprasellar cistern. When choosing an approach to lesions in this area, it is important to note the location of the carotid arteries and the direction of tumor extension. The transnasal transsphenoidal approach is preferred for access to the majority of pituitary adenomas. It offers direct access to the sella and its contents with no brain retraction and minimal morbidity. Although the majority of cases are suitable for a transsphenoidal approach, lateral extent of tumor or ectatic carotid arteries may limit access to the tumor. The most common transcranial alternatives are the pterional or subfrontal approaches.

to the circular sinus. A transverse incision may then be made in the dura rostral and caudal to the circular sinus, with bipolar coagulation and transection of the circular sinus. This sinus is a structure contained between the leaves of the dura. Transection of the circular sinus then enables exposure of the suprasellar cistern itself and provides adequate room for surgical resection of tumor in this location.

Once the mass has been resected, attention must be paid to obliteration of the CSF fistula if the arachnoid has been violated (Fig. 8). During transsphenoidal procedures in which the arachnoid has been breached, we routinely harvest a fascia lata graft of appropriate size to cover the opening; the graft is placed on the intradural side of the opening (within the intrasellar compartment), and a small piece of Marlex mesh is fashioned to place intrasellar to maintain the apposition of the fascial graft. Placement of the fascial graft is critical; the intracranial pressure will tamponade the graft to the dura if properly inserted. Before closing, the anes-

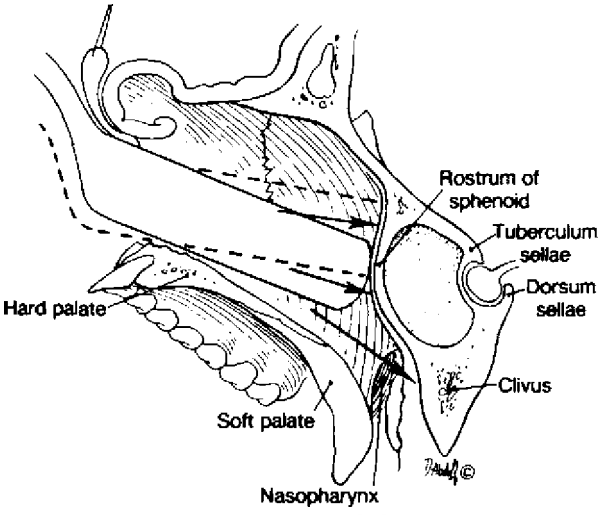

FIG. 4. Exposure via the transsphenoidal approach. One may vary the exposure from the suprasellar cistern to the lower clivus depending on the trajectory chosen via the transsnasal approach. The entire extent of the clivus may be accessed by directing the dissection inferiorly along the vomer and the roof of the hard palate. Similarly, a lesion lying over the tuberculum sellae and even the planum sphenoidal can be approached by carrying the dissection anterior to the sella turcica after the rostrum of the sphenoid has been resected.

thetist is asked to perform a Valsalva maneuver to assess the functional integrity of the graft. The sphenoid behind this graft is then packed with fat obtained at the harvest of the fascial graft to further

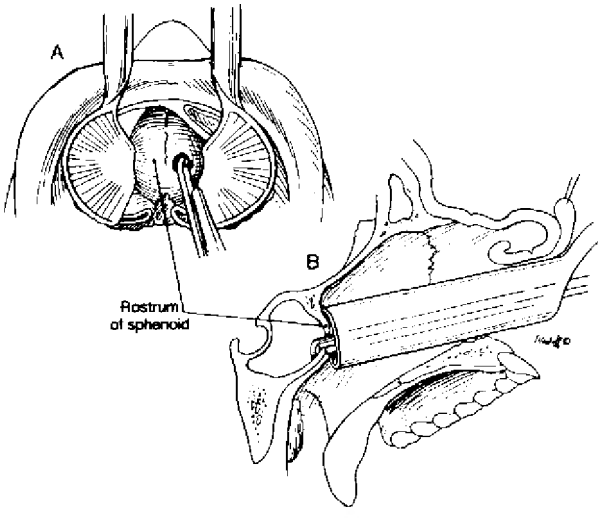

FIG. 5. Sphenoidal landmarks. A: The perpendicular plate of the ethmoid is a useful landmark to guide the surgeon to the rostrum of the sphenoid sinus. After removal of the perpendicular plate of the ethmoid, the sphenoid sinus ostia represent the anterior extent of sphenoidal exposure. B: Resection of the rostrum of the sphenoid sinus utilizing the ostia to gain access to the sella turcica. If the sphenoid sinus is nonpneumatized, one can use a high-speed drill to gain access to the sella.

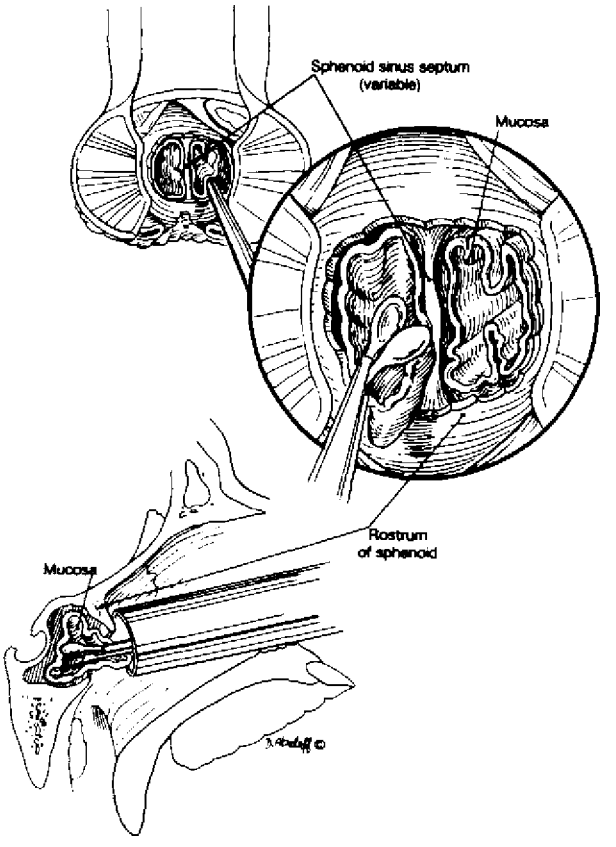

FIG. 6. Exposure of the sella. Once the rostrum of the sphenoid has been resected to allow visualization of the full extent of the sphenoid, the sphenoid sinus mucosa should be exenterated, which will help control any bleeding from this mucosa as well as avoiding the potential for a postoperative sphenoid sinus mucocele. There is almost always a bony septum within the sphenoid sinus that also must be removed to allow access to the entire extent of the floor of the sella turcica. Frequently, this septum is somewhat eccentric, and preoperative imaging may give an indication of its location. Dissection along one side of the septum only will give compromised exposure of the floor of the sella with resultant compromise to the extent of resection of the intra- or suprasellar contents.

buttress the graft in position. If there is no CSF leakage around the graft, the retractor is removed, and the posterior nasal pack is placed against the sphenoidal opening. We then perform a routine lumbar puncture (18 gauge needle) in the recovery room and on the first postoperative day to further mitigate against the development of persistent fistula. In the unusual case of a postoperative leak following this protocol, the decision to return to the operating room for a formal repacking is taken early to avoid meningitis; little is to be gained by waiting in these cases because the relatively avascular graft is less prone to spontaneous closure than in the posttraumatic situation. It has been our routine

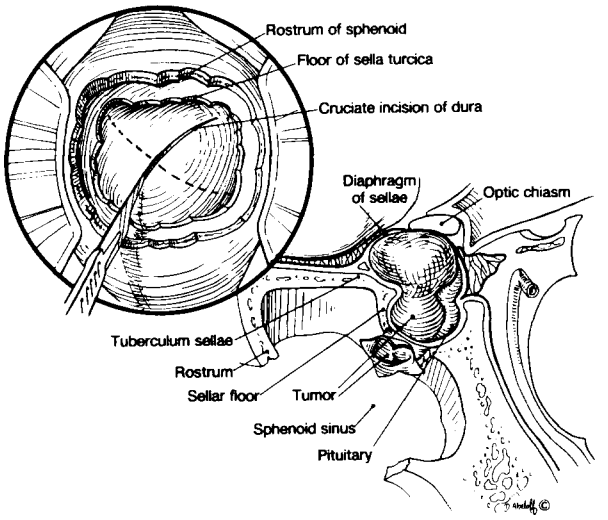

FIG. 7. Intrasellar exposure. Once the floor of the sella has been removed to identify at each lateral boundary the cavernous sinus and the circular sinus superiorly (an opening 1.5 cm square), the dura is openine in a cruciate fashion to elevate four dural flaps that give maximal surface area of exposure in the form of a square.

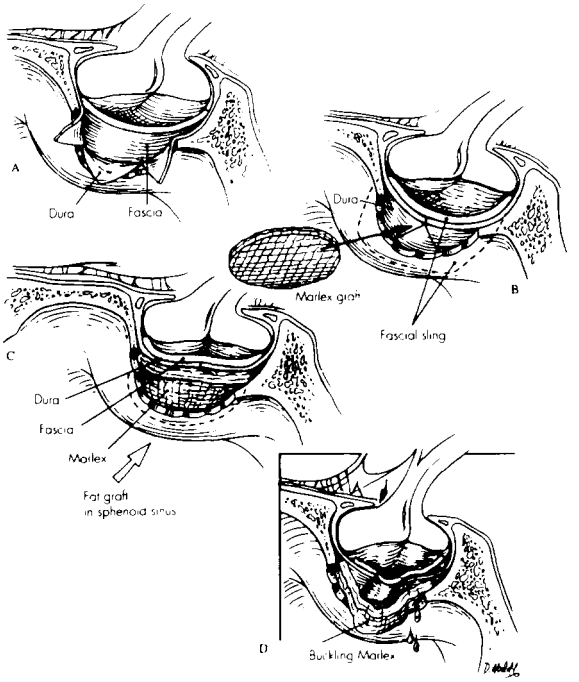

FIG. 8. Closure following tumor removal. Once the tumor mass has been resected, careful attention must be paid to closure in the event of a breach of the arachnoid, which may result in a CSF fistula. If a CSF leak is recognized at operation, a fascia lata graft is harvested. (A) The fascia is placed against the remaining pituitary gland within the intrasellar compartment. (B) Placement of the fascia graft within the sella is crucial; the graft will tamponade against the dura if placed properly. (C) This is then buttressed in place with a tailored piece of Marlex mesh just large enough to fit inside the sellar bony opening. (D) The Marlex mesh must be fitted correctly to insure graft integrity.

practice to obtain nasopharyngeal cultures prior to prepping of the nose to guide antibiotic coverage should a postoperative meningitis occur.

The remarkably low morbidity and mortality associated with transsphenoidal resection of even very large tumors have encouraged our group to consider transnasal resection as the preferred primary approach to virtually all macroadenomas. Many of these herniate into the enlarged sella from the suprasellar cistern, subfrontal space, and cavernous sinus once the sellar component has been evacuated. We have, on rare occasions, found tumors that do not enlarge the sella but grow directly into the suprasellar cistern. These may present a particular problem; but, by mobilizing normal gland and opening through the tuberculum sellae as described previously, one can frequently gain access to the suprasellar cistern and extract the tumor.

Transcranial Approach

Our experience with pituitary adenomas has enabled us to formulate a plan that essentially obviates the use of a transcranial approach for pituitary macroadenomas. On the other hand, there are limited occasions in which such an approach is desirable (165). These instances, as outlined previously, are when the transsphenoidal approach is hazardous from the presence of ectatic carotid arteries or when the tumor spills over into the middle fossa or both middle fossae while leaving a small virtually normal-sized sella turcica. Such lesions generally occur because of an incompetent diaphragma sellae that provides the vehicle for superior and lateral growth of tumor or possibly extensive anterior and/or posterior growth of tumor without the significant or measureable expansion of the sella. Under such circumstances, direct visualization of the tumor by the transcranial approach may be optimal. In addition, there are occasional cases in which the consistency of tumor encountered via the transsphenoidal approach defies an adequate resection of tumor from this approach. This may require a secondary transcranial procedure when inadequate decompression of the optic mechanism has been established. If the optic mechanism has been adequately decompressed, one would generally use postoperative RT to "mop-up" any residual tumor that may defy resection via the transnasal route.

During the course of transcranial surgery, the significant complicating anatomy presents itself primarily related to the vascular supply to the hypo-

thalamus as well as the optic chiasm and nerves and tracts (Fig. 9). Almost all pituitary tumors should lie below the arachnoid so that one would want to open the arachnoid and then stay below the arachnoid plane so as not to potentially compromise the perforating vasculature to the optic mechanism as well as the hypothalamus. The pterional approach to the suprasellar cistern lends itself best for this procedure, but one must recognize that the ipsilateral optic nerve may prevent adequate visualization of tumor extending beneath it when the tumor undergoes growth in a lateral direction. The best technique in these circumstances is an extensive decompression medial to the optic nerve followed by subsequent mobilization of the tumor from the lateral compartment underneath the optic nerve from lateral to medial so that one can mobilize this final remnant of tumor. Exquisite care must be exercised to attempt to visualize the proximal portion of the carotid artery along with its ophthalmic branch to preserve the integrity of these structures while also avoiding any disruption of the perforating vessels coming from the internal carotid artery to the posterior aspect of the optic chiasm as well as optic nerve.

The consistency of the tumor, as from below, is usually that of a soft and friable lesion that is easily debulked by the use of curettes of variable lengths and rotations. The main difficulty encountered with the removal of the lesion is the adherent capsule that may preclude total removal without injury to cranial nerves or the midline neuraxis. In such cases, it is certainly more prudent to remove the soft interior and to leave a densely adherent capsule than to risk cranial and vascular injury for a lesion that is likely not curable by surgery alone. These patients invariably need RT for ultimate tumor control. The goals of the operation should primarily be decompression of the optic apparatus and judicious tumor removal without exposing neural or vascular structures to undue risk of injury.

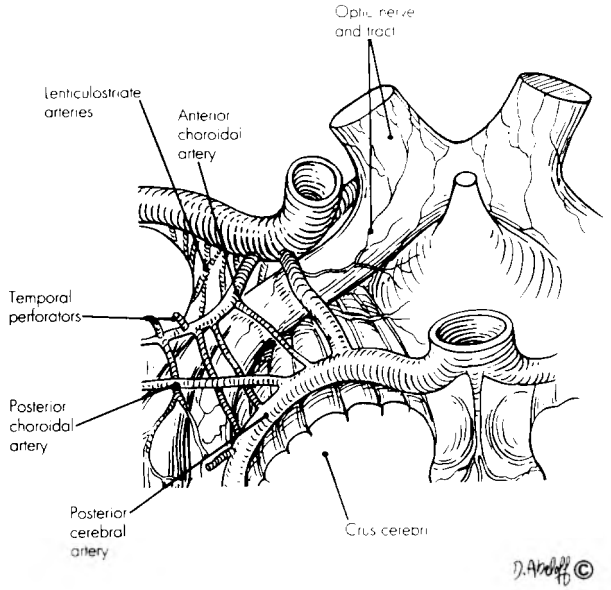

FIG. 9. Hazards with the transcranial approach. During a transcranial exposure for a tumor with suprasellar extension, one must exercise caution with the manipulation of low midline neural and vascular structures. The abundant perforating arteries in this region pose a hazard to manipulation of the adherent capsule of the pituitary tumor.

Perioperative Management

Perioperative glucocorticoids are administered to all patients; this is crucial if preoperative endocrine assessment indicates any hypocortisolemia. Methylprednisolone is given i.v. at sizable dosages of 40 mg (or 10 mg dexamethasone) every 6 h in the immediate perioperative period in those cases with neurological compromise, usually starting the day before surgery. Then a dose regimen tailored to the individual patient's projected glucocorticoid needs as anticipated by the preoperative endocrine assessment and intraoperative findings is followed. In those patients without visual compromise, lower dosages of these high-potency glucocorticoids may be employed.

Thyroid function, as mentioned previously, should be assessed preoperatively and normalized before any elective surgical intervention. The stress of surgery may provoke an acute crisis in the patient without sufficient reserve and should be a consideration in patients with an otherwise unexplained alteration in mental status postoperatively.

Serial visual field testing is routinely performed in the recovery room and ICU to monitor visual and general neurological condition. In the patient with preoperative visual deficit, careful monitoring in the early postoperative period is essential. Both the transfrontal and transsphenoidal routes are successful in improving vision. Immediate postoperative improvement of vision may occur, with a significant improvement usually $\leq$2 weeks, but continued improvement may occur for up to 12 months. More importantly, any *loss* of vision in the postoperative period may indicate an evolving hemorrhagic complication; in this instance, emergent CT scanning should be performed to exclude this. Evidence of

hemorrhage on the postoperative scan with a progressive visual deficit warrants emergent transsphenoidal reexploration.

Blood pressure is carefully monitored; hypotensive events are to be avoided, especially in cases with compressive neurological deficit in which tissue perfusion is already marginal.

Urine volumes and specific gravities must be followed in concert with sodium levels to clearly understand the dynamics of potential postoperative DI. Manipulation of the normal posterior pituitary gland may produce transient fluctuations in urine output.

Before discharge, an a.m. fasting serum cortisol is obtained to determine the need for cortisol replacement. Intraoperative evidence of residual normal pituitary gland is also a major guide in such considerations. Thyroid evaluation is usually done 3 to 4 weeks postoperatively because autonomous function of the thyroid may persist for some time postoperatively.

Unless clinically indicated, postoperative imaging is not performed for at least 6 weeks postoperatively—3 months in most cases. This allows clearance of all operative artefactual changes that might confuse one's decision about the implementation of postoperative adjuvant therapy.

RADIOTHERAPY FOR PITUITARY ADENOMAS

Postoperative RT

The rationale for the use of postoperative RT is to reduce the incidence of recurrence; several studies suggest improved tumor control with the combination of surgery plus RT (158,167,168). This is especially true in large and invasive lesions, which manifest an increased rate of recurrence. This treatment does not ensure recurrence-free survival, but the time to recurrence may be prolonged. Valtonen and Myllymaki (169) have reported a surprisingly high 36% recurrence rate in patients with a "total removal" following transfrontal craniotomy and postoperative RT, with recurrences occurring $\geq$18 years after therapy. Thus, published recurrence rates may be misleading in series with short follow-up times. This is an important consideration; morbidity and mortality both increase with operative intervention in cases of recurrence (169,170).

With functioning pituitary tumors, evaluation of postoperative endocrine status may give indication about the effectiveness of the surgical removal; however, in nonfunctioning lesions, the judgment of the surgeon supplemented by postoperative imaging are the only parameters to gauge the extent of resection and therefore risk of recurrence. The surgeon's appreciation of the totality of the resection may not be accurate in the face of an invasive tumor. The lack of a chemical marker in a true nonfunctional tumor makes assessment of cure difficult in the postoperative period. Furthermore, in contrast to PRL- and GH-secreting tumors, no adjunctive pharmacotherapy is available.

For these reasons, the criteria for selection of patients for postoperative RT remains controversial. In general, large tumors, which have a high frequency of invasion of the cavernous sinus and dura and therefore defy complete surgical excision, should all be considered candidates for postoperative RT, especially if the patient is hypopituitary postoperatively. Similarly, with frank cavernous sinus invasion, postoperative RT is advocated. In those cases where tumor invasion is not evident and "total" removal has been achieved, following the patient with routine scanning on a yearly basis may be an appropriate strategy, especially if endocrine function is intact.

The recent development of stereotactic radiosurgery (image-directed focal RT) may provide a safer and more effective method of RT for pituitary adenomas. Focused RT may potentially avoid damage to midline neural and vascular structures while delivering high local therapeutic doses to the lesion with great accuracy. Results from current ongoing clinical trials are forthcoming.

Primary RT

RT was advocated for the management of pituitary tumors as early as 1907 (138). In the elderly patient or any patient harboring a medical illness that may pose a significant risk to general anesthesia and surgery, consideration should be given to primary RT, after an appropriate clinical diagnosis of a pituitary tumor. Fortunately, with the extremely low morbidity and mortality rates reported in published series from experienced surgeons, the number of patients referred for primary RT is low. The indications for this nonsurgical approach strengthen in cases with hypopituitarism.

Reported series of patients treated with RT alone describe a 50% recurrence rate with a 75% local control following salvage treatment (158). Other authors report a local control rate of 50 to 79%, with

an adequate salvage in cases of recurrence (171, 172). A dose of 4000 Gy by external beam is considered optimal by most radiotherapists (173,174). Recently it has been suggested that late recurrence after RT, which occurs not uncommonly, may be the result of inadequate dosage. Treatments with 4500 Gy given in 25 fractions have been reported to result in a high (>90%) probability of stable long-term control (175).

RT, however, should not be considered a completely benign therapy or an equivalent alternative to microsurgical resection. Adverse effects from radiation in this region may range from mild to severe. It carries a significant risk of worsening preexisting hypopituitarism, with an overt 10 to 15% frequency of panhypopituitarism (168). It may increase the rate of atherogenesis in the major vessels in the field and cause visual impairment (158). These complications increase as a function of total treatment dose (173). The visual impairment may result from one of several mechanisms, including empty sella syndrome, treatment failure, or direct radiation damage to optic pathways. This latter complication is seen with significant frequency with daily fractionation >220 Gy (173). Other minor complications from RT include epilation, scalp swelling, and otitis (176).

Acknowledgment: Portions of this paper were adapted from references 43, 90, and 166.

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